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August 24, 1998

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Jane Axelrad
Mail Code HFD5
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Ms Axelrad:

Thank you for your kind invitation to participate in the FDA Workshop on PET radiopharmaceuticals to be held in Rockville on August 27, 1998. The PET Radiopharmaceutical Committee (PET RC) will be represented at the meeting by Dennis Swanson (U Pittsburgh), Peter Conti (USC), Jerry Kuhs (PET Net) and myself (UCLA). I also anticipate other members of the PET community to attend the meeting.

I'm enclosing with this correspondence a position document on PET radiopharmaceutical regulation and clinical indications drafted by the PET Radiopharmaceutical Committee. This document evolved from the Committee after extensive consultation with the Institute of Clinical PET, the Society of Nuclear Medicine, the American College of Nuclear Physicians and others. It represents a consensus position among their members.

I would like to submit for your consideration the possibility of discussing elements of our document with you and your staff at the meeting. I do not suggest changing the agenda proposed for the meeting, that is indeed very appropriate and relevant, but perhaps adding a section for discussion if you feel it is feasible. In any case, I'm sure we will have opportunities in the near future to discuss the subject in detail.

Again, thank you for the opportunity to meet with you and your staff again.

Sincerely,

Jorge R. Barrio
Chair, PET RC

cc: J. Keppler, ICP

98D-0266

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PROPOSED REGULATORY FRAMEWORK FOR POSITRON EMISSION TOMOGRAPHY (PET) RADIOPHARMACEUTICALS

(IMPORTANT NOTE: This document evolved from the PET Radiopharmaceutical Committee after extensive consultation with the Institute of Clinical PET, the Society of Nuclear Medicine, the American College of Nuclear Physicians and others. It represents a consensus position among their members)

Introduction

Section 121 of the Food and Drug Administration Modernization Act of 1997 (FDAMA), Pub. L. 105-115, requires that the Food and Drug Administration (FDA) establish:

> (i) appropriate procedures for the approval of positron emission tomography drugs pursuant to section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355), and
> (ii) appropriate current good manufacturing practice requirements for such drugs.

Section 121(c)(1)(A). In addition, Congress provided that:

> In establishing the procedures and requirements required by subparagraph (B), the Secretary of Health and Human Services shall take due account of any relevant differences between not-for-profit institutions that compound the drugs for their patients and commercial manufacturers of the drugs.

Section 121(c)(1)(B).[1] The Secretary is directed to consult with patient advocacy groups, professional associations, manufacturers, and physicians and scientists who make and use PET drugs prior to establishing the procedures and requirements. *Id.*

To assist FDA in carrying out its consultation responsibilities under Section 121, an ad hoc Committee consisting of representatives of the Institute of Clinical PET, the Society of Nuclear Medicine and the American College of Nuclear Physicians has prepared this document. The Committee includes members from the commercial PET community as well as from not-for-

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[1] Section 121 also provides that FDA shall not require the submission of new drug applications or abbreviated new drug applications for compounded positron emission tomography drugs that are not adulterated for a period of four years after the enactment of FDAMA or two years after FDA establishes the procedures and requirements contemplated by Section 121, whichever comes later.

profit institutions. The Committee has joined together to propose a coherent, reasonable and achievable approach to the production of PET drugs which will protect the interests of patients and not impose unnecessary and possible crippling requirements on not-for-profit institutions.

Background

PET is an imaging procedure that employs very small amounts of injected radioactive substances (radiopharmaceuticals) for the purposes of obtaining:

- fundamental information on physiological and pathophysiological processes and the pharmacokinetics and pharmacodynamics of drug substances; and
- diagnostic information pertinent to the clinical management of patients with various diseases and conditions

Human research studies incorporating PET techniques have been performed for more than twenty years resulting in thousands of scientific papers in the literature. Positron-emitting labeled radiopharmaceuticals have also been used for more than fifty years in humans for clinical indications (i.e., [F-18]sodium fluoride as a bone metabolism agent).

An underlying principle of PET radiopharmaceutical techniques is that the radioactive substance used to evaluate the metabolic or physiologic process must not alter the process it is attempting to measure. Moreover, PET radiopharmaceuticals commonly incorporate radionuclides of elements encountered in nature possessing ultra-short half-lives (e.g., the physical half-life of O-15 = 2 minutes; N-13 = 10 minutes; C-11 = 20 minutes; F-18 = 110-minutes). Most PET radiopharmaceuticals are thus radiolabeled versions of substances commonly present in the body (e.g., [N-13]ammonia, [O-15]water; [C-11]acetate; [C-11]methionine) or in the water supply (i.e., [F-18] sodium fluoride). Alternatively, they could be close relatives or analogs of natural enzyme substrates (e.g., [F-18]fludeoxyglucose, [F-18]fluoroDOPA) or drugs of common use (e.g., [C-11]flumazenil).

Several principles surrounding the use of PET radiopharmaceuticals have been established:

Existing PET radiopharmaceuticals that are currently used in clinical practice do not produce physiological or pharmacological effects and are inherently safe. There have been neither documented reactions of clinical significance nor death resulting from the administration of such PET radiopharmaceuticals after several millions of studies performed in humans worldwide.

There are no radioactive waste problems associated with the use of these radiopharmaceuticals.

The amount of radiation exposure that a human subject receives from a PET imaging procedure is only a fraction of the radiation exposure permitted to radiation workers (e.g., X-ray technologists) on an annual basis.

With that background, the committee proposes that FDA regulate PET centers in the following manner.

Not-for-profit Institutions

Congress, through FDAMA, has appropriately recognized that institutions and physicians that prepare PET radiopharmaceuticals on a "not-for-profit" basis for use solely in the care of their patients are subject to a differing set of fiscal constraints and concerns compared with commercial entities that distribute PET radiopharmaceuticals on a for-profit basis. Moreover, many of the former institutions have invested extensively in equipment, facilities, and personnel to support initial and continuing research on or involving this technology; and these institutions should be allowed to utilize, with minimal additional encumbrance, their existing resources to address the clinical applications of PET.

It is proposed that a "not-for-profit radiopharmaceutical production facility" be defined as an entity or component of an entity that prepares PET radiopharmaceuticals on a not-for-profit basis, solely for use in the care of the entity's patients.

Any facility that does not meet the definition of a "not-for-profit PET radiopharmaceutical production facility" shall be referred to as a "commercial PET radiopharmaceutical production facility".

FDA Registration

1. Commercial PET radiopharmaceutical production facilities shall register their establishments with the FDA pursuant to Section 510(b) of the FD&C Act and shall list the PET radiopharmaceuticals produced by the facility in accordance with Section 510(j) of this act.

2. Not-for-profit PET radiopharmaceutical production facilities shall be exempt from the requirement to register as a drug establishment with the FDA in accordance with Section 510(g) of the FD&C Act.

a. Not-for-profit PET radiopharmaceutical production facilities shall register with the FDA through their establishment of, or affiliation with, a PET Radioactive Drug Committee (PRDC). The requirements for the PRDC shall be codified in the FDA regulations and appropriately modified from the requirements for a Radioactive Drug Research Committee (RDRC, see 21 CFR 361.1), but expanded to include oversight of both the

basic research and clinical applications of PET radiopharmaceuticals. (Note: Consistent with current 21 CFR 361.1 regulations, an evaluation of the safety and efficacy of a new PET radiopharmaceutical for a proposed clinical indication must occur under an IND exemption approved by the FDA.) The PRDC shall provide the FDA, on an annual basis, a list of PET radiopharmaceuticals used clinically by each of the not-for-profit radiopharmaceutical production facilities operating under its jurisdiction. (Note: this listing of PET radiopharmaceuticals for clinical use shall be separate from, and in addition to, the annual listing of PET radiopharmaceuticals used for basic research studies.)

b. Not-for-profit PET radiopharmaceutical production facilities that do not wish to establish or affiliate with a PRDC may register with the FDA as a drug establishment (i.e., pursuant to Sections 510(b) and (j) of the FD&C Act).

Standards Applicable to the Production of PET Radiopharmaceuticals

The FDA, in its Federal Register notice dated February 27, 1995 (60 FR 10517), recognizes that "PET manufacturing procedures differ in a number of important ways from those associated with the manufacture of conventional drug products", and that "Part 211, Current Good Manufacturing Practice Standards (cGMPs), which are primarily directed to the regulation of conventional drug products, contain requirements and specific language which might result in unsafe handling of PET radiopharmaceuticals, are inapplicable or inappropriate, or which otherwise do not enhance drug product quality in the manufacture of PET radiopharmaceuticals".

It must also be recognized that the majority of existing PET facilities (involved in either the not-for-profit or commercial production of PET radiopharmaceuticals) were not established with the intent of having, in the future, to comply with the FDA's cGMPs, nor are they staffed with individuals who have extensive experience with these requirements. Thus the Committee feels that it is important that a mechanism be established to permit standards specific to the production of PET radiopharmaceuticals to evolve from the PET community (i.e., consistent with the evolution of the FDA's cGMP requirements from the pharmaceutical industry). The Committee also feels that it would be difficult to justify to the public two sets of standards for the production of PET radiopharmaceuticals, i.e., one set of standards applicable to not-for-profit PET radiopharmaceutical production facilities and a separate set of standards for commercial PET radiopharmaceutical production facilities. Hence, it is felt that there should be a single set of standards for the production of PET radiopharmaceuticals; the initial version of these standards being of appropriate intensity to ensure adequate PET radiopharmaceutical quality and safety, yet permitting compliance by all existing PET facilities.

Based on these considerations, the Committee recommends that all facilities involved in the production of PET radiopharmaceuticals be required to comply with respective US Pharmacopoeia (USP) monographs and with the current USP chapter on the compounding of PET radiopharmaceuticals. (Note: FDAMA currently recognizes the USP monographs and compounding chapter as providing acceptable standards for the production of these agents). The USP compounding chapter has been rendered an "Official Chapter" within the USP, thus making

its provisions enforceable by the FDA. The USP Committee of Revision also provides a mechanism whereby the standards for the production of PET radiopharmaceuticals can evolve rapidly with active input from both the FDA and the PET community. These standards should be developed with the intent that they be applicable to both PET radiopharmaceuticals intended for research use and PET radiopharmaceuticals intended for clinical use, since it does not make sense to have one set of production standards for a given agent when used in the research setting versus a different set of standards when the same agent is used in the clinical setting. Within an agreed upon time frame, these USP compounding standards should be codified within the FDA regulations as specific current good manufacturing standards for PET radiopharmaceuticals.

Compliance Monitoring

1. Commercial PET radiopharmaceutical production facilities and other facilities registered with the FDA in accordance with Sections 510(b) and (j) of the FD&C Act shall be inspected for compliance with the USP compounding standards and monographs pursuant to the FDA's existing requirements for registered drug establishments addressed under Section 704 of the FD&C Act.

2. For not-for-profit PET radiopharmaceutical production facilities, monitoring of compliance with USP compounding standards and monographs shall be the responsibility of the PRDC having jurisdiction over the facility. (Note: As per the 21 CFR 361.1 regulations, RDRC activities are subject to inspection by the FDA and this will also apply to FDA regulations addressing PRDCs. The Committee recommends however, that the FDA exercise discretion in its inspection policy respective to PRDC activities so that such inspections would be initiated based only for cause. It is further noted that not-for profit PET radiopharmaceutical production facilities will continue to qualify for exemption from certain of the FDA's inspection procedures in accordance with Section 704 of the FD&C Act).

NDAs/ANDAs for PET Radiopharmaceuticals

1. The Committee believes that no good purpose would be served by requiring traditional new drug applications (NDAs) to be filed for PET radiopharmaceuticals that have been prepared and used successfully and safely for many years, and that have been recognized by experts in the field as being safe and effective for certain specific clinical indications. Accordingly, the Committee proposes that the FDA grant NDA status to the following five PET radiopharmaceuticals, for which USP monographs have been previously developed.

    1. F-18 Fludeoxyglucose (FDG),
    2. F-18 Sodium Fluoride,
    3. F-18 FluoroDOPA,
    4. N-13 Ammonia, and
    5. O-15 Water.

The Committee further proposes that NDA status granted to these well-established PET radiopharmaceuticals extend to the clinical indications for each agent as published in the USP-DI, these clinical indications reflecting the community standard of practice and the opinion of experts in the field. It is recognized that continued support for the publication of the USP-DI may cease in the near future. Thus, if a USP-DI monograph does not currently exist for one or more of these 5 well-established agents, appropriate clinical indications for the respective agent(s) shall be identified by a PET radiopharmaceutical advisory committee or task force established by the FDA.

Subsequent to the FDA granting NDA status to these well-established PET agents, a commercial PET radiopharmaceutical production facility would be required to submit an abbreviated NDA (ANDA) for each of these agents it wishes to prepare and distribute for clinical use. Information submitted under these ANDAs should be limited to addressing respective chemistry and manufacturing data, labeling and controls (i.e., to be in compliance with USP monographs and compounding standards). Not-for-profit PET radiopharmaceutical production facilities would not be required to submit ANDAs for these agents.

2. For new PET radiopharmaceuticals (i.e., other than the five well-established agents identified above), a NDA must be submitted to, and approved by, the FDA prior to distribution of the new PET radiopharmaceutical for routine clinical use. (Note: evaluations of the safety and efficacy of new PET radiopharmaceuticals for proposed clinical indications must be conducted under an IND exemption approved by the FDA.) A NDA for a new PET radiopharmaceutical may be submitted by a commercial PET radiopharmaceutical production facility, or by a not-for-profit PET radiopharmaceutical production facility.

a. With FDA approval of a NDA for a new PET radiopharmaceutical, a commercial PET radiopharmaceutical production facility will be permitted (i.e., subject to addressing patent or exclusivity provisions) to distribute the PET radiopharmaceutical for clinical use subsequent to 1) its submission and FDA approval of an ANDA for the respective agent; or 2) its independent submission and FDA approval of a NDA for the respective agent.

b. With FDA approval of a NDA for a new PET radiopharmaceutical, not-for-profit PET radiopharmaceutical production facilities will be permitted (i.e., subject to addressing patent or exclusivity provisions) to distribute the PET radiopharmaceutical for clinical use with no ANDA or NDA submission requirements. The PRDC having jurisdiction over the not-for-profit facility will have responsibility ensuring that a NDA had been approved for the new PET radiopharmaceutical, that appropriate manufacturing standards, labeling and controls are in place for the new PET radiopharmaceutical and that it is being used clinically for appropriate established indications.

c. It is recognized that many PET radiopharmaceuticals have and will continue to be utilized extensively in the research setting in accordance with current 21 CFR 361.1 regulations (and the proposed PRDC regulations.) The committee recommends that a mechanism exist for the submission and FDA approval of a "paper NDA" to permit routine clinical use of such extensively utilized PET radiopharmaceuticals. Such paper NDAs are likely to be dependent on data submitted by a consortium of not-for-profit and commercial PET radiopharmaceutical production facilities and no patent rights, nor commercial exclusivity can be claimed. With FDA approval of a paper NDA for a new PET radiopharmaceutical, commercial and not-for-profit PET radiopharmaceutical production facilities may distribute the agent for clinical use subsequent to fulfilling the requirements addressed in 2a and b above.

3. In enacting Section 121 of FDAMA, Congress directed the FDA to develop "appropriate procedures for the approval of positron emission tomography drugs pursuant to section 505 of the Federal Food, Drug and Cosmetic Act." The Committee believes that the appropriate procedures for such approval must take into account the very limited radioactivity dosages employed and radiation exposures involved; the fact that PET radiopharmaceuticals will not be administered on a chronic basis; that these agents are, in general, devoid of physiological effects; and that the information derived from PET studies is typically used in conjunction with information from other diagnostic and clinical information to elicit a benefit to the patient. Accordingly, FDA's traditional requirements for the safety and efficacy of new therapeutic drugs are largely inappropriate for PET radiopharmaceuticals. The Committee believes that FDA's proposal for regulation of non-PET diagnostic radiopharmaceuticals, published in the Federal Register of May 22, 1998 (62 FR 28301) forms an appropriate basis for similar regulation governing the approval of PET radiopharmaceuticals. However, separate regulations and guidelines for the approval of PET radiopharmaceuticals may have to be prepared consistent with Section 121 of FDAMA, if the final FDA regulations and guidelines for non-PET diagnostic radiopharmaceuticals cannot be appropriately applied to PET radiopharmaceuticals.